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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,535	MURPHY ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,9,12-19,21-48 and 53-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,9,12-19,21-48 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to Applicants' response, filed on June 25, 2004. Currently, claims 1, 4-7, 9, 12-19, 21-48 and 53-57 are pending and are rejected herein.

2. This action contains new rejections that are not necessitated by Applicants' amendment and therefore, this action is made NON-FINAL. Any rejections not reiterated herein are hereby withdrawn. Specifically, the Volkov rejection has been withdrawn in view of Applicants' arguments, as Volkov does not teach a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid. In addition, the rejections of Short and Stemmer have been modified in view of Applicants' amendments and arguments.

Declaration Under 37 CFR 1.131

3. It is noted, the declaration filed on June 25, 2004 under 37 CFR 1.131 has been considered but is ineffective to overcome the Volkov reference. The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Volkov reference. Specifically, the declaration does not state the invention was reduced to practice in this country or a NAFTA or WTO member country. However, as noted above, the Volkov rejection has been withdrawn for other reasons.

Claim Rejections - 35 USC § 112 – First Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4-7, 9, 12-19, 21-48 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to "adding at least one dideoxynucleotide analog." The specification states, "the term...analog...refers to a molecule that may or may not structurally resemble *a naturally occurring molecule*, but functions similarly *to the naturally occurring molecule.*" See page 23, lines 6-8. However, a dideoxynucleotide is not a naturally occurring analog. Furthermore, Applicant has not described any "dideoxynucleotide analogs" by structure or function.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed.*" See page 1117.

> Possession may be shown in many ways. For example, possession may be shown, *inter alia,* by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas, which permit a person skilled in the art to clearly recognize, that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention...
>
> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that

> distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient...In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. In contrast, for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession." (Federal Register/Vol. 66, No. 4/Friday, January 5, 2001/Notices; p. 1105-1106).

Accordingly, because the specification does make clear that Applicants were in possession of the claimed invention at the time the application was filed, the specification does not describe by structure or function what a "dideoxynucleotide analog" is, and because a dideoxynucleotide is not a naturally occurring molecule, the claims lack adequate written description.

Applicant's attention is also drawn to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1st Paragraph, Written Description Requirement" (published in Federal Register/Vol. 66, No. 4/Friday, January 5, 2001/Notices; p. 1099-1111).

Claim Rejections - 35 USC § 112 – First Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 4-7, 9, 12-19, 21-48 and 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 4-7, 9, 12-19, 21-48 and 57 are indefinite because it is not clear as to what encompasses a "dideoxynucleotide analog." The specification states, "the term...analog...refers to a molecule that may or may not structurally resemble *a naturally occurring molecule*, but

functions similarly *to the naturally occurring molecule*." See page 23, lines 6-8. However, a dideoxynucleotide is not a naturally occurring analog. Accordingly, because a dideoxynucleotide is not a naturally occurring molecule, it is not clear as to what constitutes a "dideoxynucleotide analog."

B) Claim 56 is indefinite because it is not clear how one modifies or removes the Maxam and Gilbert treatment or variant thereof, if a further extension is to be performed. The specification teaches the Maxam and Gilbert treatment allows for cleavage at naturally occurring nucleotides. See page 37, lines 9-10. However, it is not clear from the specification as to how one skilled in the art would modify or remove the Maxam and Gilbert treatment, if a further extension is to be performed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 53-54 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Short et al. (WO 98/01581, cited in the IDS).

Short teaches a method for creating a nucleic acid comprising the steps of:

(a) annealing a defined primer nucleic acid to at least one first single stranded template nucleic acid,

(b) performing a first extension by extending the primer nucleic acid employing the first template nucleic acid to form an extended nucleic acid,

(c) denaturing the extended nucleic acid from the first template nucleic acid,

(d) annealing the extended nucleic acid to at least a second single stranded template nucleic acid whose sequence is not identical to the first template nucleic acid,

(e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid,

(f) adding at least one length-altering agent before or during at least one of the first extension or the second extension, and

(g) modifying or removing the length-altering agent from the extended nucleic acid, if a further extension is to be performed. See pages 7-9, 12, 15, 18, 25-35, 38-39, 45 and 67-68, for example.

With respect to the limitation of "length-altering agent," the specification states, "the term 'length-altering agent' means an agent that may either terminate chain-elongation or be used to later shorten an extended nucleic acid (e.g., a chemical agent). In specific aspects, the length-altering agent may comprise a nucleotide, a modified nucleotide or a nucleotide analog." See page 34, lines 19-22.

Short teaches the use of DNA adducts, DNA intercalating agents, DNA binding proteins, triple helix forming agents, competing transcription polymerase, nucleotide analogs, chain terminators, and polymerase inhibitors or poisons, which are considered to encompass the recitation of "length-altering agent." See pages 8, 33-34 and 67. Specifically, Short teaches numerous examples of DNA adducts, for example, (including those with an "alkaline condition")

which block or interrupt the amplification process. See page 8. Furthermore, Short teaches the use of nucleotide analogs (including at least one ribonucleotide, e.g., 5-bromouracil) that can also be used to block or interrupt amplification (see pages 33-34 and 67). Finally, Short teaches that chain terminators are used to block or interrupt polynucleotide synthesis or amplification. See page 67. Dideoxynucleotides are considered to be (and therefore an inherent property of) "chain terminators." See, for example, Rosenthal et al. (USPN 6,087,095, col. 5, lines 38-54, previously cited), and Monforte et al. (USPN 5,830,655, col. 9, lines 39-40 and col. 35, line 39) who teach that dideoxynucleotides are chain terminators.

The reference is directed to producing polynucleotides by interrupting polynucleotide synthesis using a "length-altering agent," followed by specific, self-primed primer extension. See pgs. 7 and 67, for example. The first step, interrupting polynucleotide synthesis, encompasses both random and non-random primer extension because Short does not limit the polynucleotide synthesis to only random amplification. See pages 7 and 67, for example. During the interrupting step, fragments of different length of the polynucleotide are being generated, creating "resultant polynucleotides." See page 7. Following the interrupting step, single or double stranded polynucleotides are added to the resultant polynucleotide fragments, wherein the added polynucleotides comprise an "area of identity in an area of heterology" to one or more of the resultant polynucleotide fragments (i.e., these added polynucleotides are of a defined sequence, and will anneal to a defined region). See page 7. Following the annealing of the defined polynucleotides (i.e., defined primer), the polynucleotides are incubated, thus performing linear primer extension.

Thus, Short teaches that the addition of a "length-altering agent" occurs **before** the annealing of a defined primer nucleic acid to at least one first template nucleic acid. However, it is also inherent that while some of the added polynucleotides (i.e., defined primers) are annealing to some resultant polynucleotides, some of the resultant polynucleotides are simultaneously are still being generated addition of chain terminators. That is, since some of the resultant fragments will be small, they will be generated more quickly, and therefore, will begin annealing to the added polynucleotides, while some of the larger resultant fragments are still being generated interrupted by the chain terminators. Thus, Short also teaches that the addition of the chain terminator also occurs **during** the at least one of the first extensions.

Applicants' Arguments

Applicants argue Short does not teach defined primers, a second template nucleic acid whose sequence is not identical to the first template nucleic acid, or adding at least one chain terminating agent incorporated into the extended nucleic acid. Furthermore, Applicants allege that Short is not enabling because Short does not provide guidance concerning defined primers, incorporating and then removing dideoxynucleotides or dideoxynucleotide analogs, or using a second template not identical to the first template.

Response to Applicants' Arguments

Applicants' arguments have been considered, but are not persuasive for several reasons. First, claims 53-55 and 57 do not require incorporating and then removing dideoxynucleotides or dideoxynucleotide analogs. Specifically, these claims only require the addition of at least one "length-altering agent" and modifying or removing said agent, which is taught by Short. See above. Next, Short teaches that a second template nucleic acid whose sequence is not identical

to the first template nucleic acid, since Short only requires the templates have an "area of heterology" or "region of identity," which would therefore encompass using templates having non-identical sequences. See above and pages 7-9 and 15-18. In addition, the recitation of "defined primer" does not distinguish the primers of the claimed invention from the teachings of Short. First, there is no explicit definition of "defined primer" in the specification. Applicants argue Figure 1 and page 38, line 23 to page 39, line 7 provides a description of defined primers. However, these cited passages do not provide any explicit definition as to what is meant, encompassed, included or excluded by the recitation of "defined primer." Furthermore, the specification does not limit the recitation of "defined primer" to any particular primer structure. Accordingly, because there is no specific definition of "defined primers" in the specification, this recitation has been interpreted broadly so as to encompass any primer. The express definition of "primers" contained on page 26, lines 21-23, states, "the term 'primer nucleic acid' or 'primer' is meant to encompass *any* nucleic acid that *may* anneal to a template nucleic acid, thereby initiating the synthesis of a nascent nucleic acid from the end of the primer." As Applicant has previously acknowledged, Short teaches primers that would meet this definition. Furthermore, it is also noted that Short does not limit his teachings to using "undefined" primers. For example, on page 7, lines 4-6; page 34, line 28 to page 35, line 3; page 38, lines 10-15; page 39, lines 3-6; page 41, lines 25-28; page 47, lines 6-20, Short teaches incorporating specific nucleic acids into the primers for use in extending particular templates. It is also noted, the claims use of the recitations "first extension" is relative, and therefore, a "first" extension reaction can be considered to be the first specific, self-primed primer extension (see above).

10. Claims 53-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Carr et al. (US 2001/0044111 A1).

Carr teaches a method for creating a nucleic acid comprising the steps of:

(a) annealing a defined primer nucleic acid to at least one first single stranded template nucleic acid,

(b) performing a first extension by extending the primer nucleic acid employing the first template nucleic acid to form an extended nucleic acid,

(c) denaturing the extended nucleic acid from the first template nucleic acid,

(d) annealing the extended nucleic acid to at least a second single stranded template nucleic acid whose sequence is not identical to the first template nucleic acid,

(e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid,

(f) adding at least one length-altering agent before or during at least one of the first extension or the second extension, and

(g) modifying or removing the length-altering agent from the extended nucleic acid, if a further extension is to be performed. See paragraphs 9, 12, 13, 29-32, 45-58, 75-82, 88, 89, and 128, for example.

Carr also teaches that second or subsequent rounds of extension can be achieved by the incorporation of modified nucleotides (e.g., a length-altering agent), which become cleavage points within the nucleic acid into which they are incorporated. See paragraph 51. Specifically, Carr teaches the method wherein the length-altering agent is a ribonucleotide, and wherein it is modified or removed if a further extension is to be performed (e.g., by an endonuclease). See

paragraphs 51-52. Carr further teaches the template can be of different sizes and sequences. See paragraphs 34, 47-53, 57, and 81-82, for example.

11. Claims 53-54 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative obvious under 35 U.S.C. 103 over Stemmer, W. (USPN 6,506,603).

Stemmer teaches a method creating a nucleic acid comprising;

(a) annealing a defined primer nucleic acid to at least one template nucleic acid;

(b) performing a first extension by extending the primer nucleic acid employing the template nucleic acid to form an extended nucleic acid;

(c) denaturing the extended nucleic acid from the template nucleic acid;

(d) annealing the extended nucleic acid to at least a second template nucleic acid;

(e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid;

(f) adding at least one length-altering agent, before or during at least one of the first or second extension, and

(g) modifying or removing the length-altering agent from the extended nucleic acid, if a further extension is to be performed. See cols. 4-6, 10, 15, 22-31, and 123-130, for example.

Specifically, with respect to steps (f) and (g), Stemmer teaches the addition of a uracil into the extended nucleic acid sequence, which is later modified or removed by using UDG-glycosylase. See col. 10, lines 20-25.

Applicants' Arguments

Applicants argue Stemmer does not teach using defined primers (but rather teaches gene shuffling, which involves the random fragmentation of nucleic acid sequences), a second template nucleic acid whose sequence is not identical to the first template nucleic acid, or adding dideoxynucleotides or dideoxynucleotide analogs into the extended nucleic acid and then removing said dideoxynucleotides or dideoxynucleotide analogs.

Response to Applicants' Arguments

Applicants' arguments have been considered, but are not persuasive for several reasons. First, claims 53-54 do not require incorporating and then removing dideoxynucleotides or dideoxynucleotide analogs. Specifically, these claims only require the addition of at least one "length-altering agent" and modifying or removing said agent, which is taught by Stemmer. See above. Next, Stemmer teaches that a second template nucleic acid whose sequence is not identical to the first template nucleic acid. See col. 15, lines 40-50 and col. 23, lines 22-29, for example. Furthermore, the recitation of "defined primer" does not distinguish the primers of the claimed invention from the teachings of Stemmer. See above for discussion of "defined primer." Specifically, because there is no specific definition of "defined primers" in the specification, this recitation has been interpreted broadly so as to encompass any primer. Stemmer teaches the use of primers. See above.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 4-7, 9, 12-17, 21-22, 29-30, 32, 34-41, 43-44, 47 and 57 rejected under 35 U.S.C. 103(a) as being unpatentable over Carr et al. (US 2001/0044111 A1), as applied to claims 53-54 above.

The teachings of Carr are presented above and are incorporated herein. Specifically, Carr teaches that second or subsequent rounds of extension can be achieved by the incorporation of modified nucleotides (e.g., a length-altering agent), which become cleavage points within the nucleic acid into which they are incorporated. See paragraph 51. Thus, once the length-altering agent is incorporated, only through the modification or removal of said agent will subsequent rounds of extension be possible.

Carr teaches the claimed method wherein the length-altering agent is a dideoxynucleotide. See paragraph 53.

While Carr does not specifically exemplify the modification or removal of the dideoxynucleotide, it would have been obvious to one of skill in the art, at the time the invention was made, to have modified or removed the dideoxynucleotide (e.g., by an exonuclease) in order to have achieved the benefit of conducting further rounds of extension as taught by Carr. See paragraph 51.

14. Claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-40, 43-44 and 47 are rejected under 35 U.S.C. 103(a) as being anticipated by Short et al. (WO 98/01581, cited in the IDS), in view of Short et al. (USPN 6,361,974).

The teachings of Short '581 are presented above and are incorporated herein. In addition, Short teaches a method creating a nucleic acid comprising;

(a) annealing a defined primer nucleic acid to at least one template nucleic acid;

(b) performing a first extension by extending the primer nucleic acid employing the template nucleic acid to form an extended nucleic acid;

(c) denaturing the extended nucleic acid from the template nucleic acid;

(d) annealing the extended nucleic acid to at least a second template nucleic acid;

(e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid;

(f) denaturing the twice extended nucleic acid from the second template nucleic acid;

(g) annealing the twice extended nucleic acid to a third template nucleic acid;

(h) performing a third extension by extending the twice extended nucleic acid employing the third template nucleic acid to form a thrice extended nucleic acid:

f) adding at least one dideoxynucleotide or dideoxynucleotide analog before or during at least one of the first extension, second extension, or third extension, wherein said dideoxynucleotide or dideoxynucleotide analog is incorporated into said extended nucleic acid See pages 7-9, 12, 15, 18, 25-35, 38-39, 45 and 67-68, for example.

With respect to the limitation of "at least one dideoxynucleotide or a dideoxynucleotide analog," Short teaches the use of DNA adducts, DNA intercalating agents, DNA binding proteins, triple helix forming agents, competing transcription polymerase, nucleotide analogs, chain terminators, and polymerase inhibitors or poisons, which are considered to encompass the recitation of "at least one dideoxynucleotide or a dideoxynucleotide analog." See pages 8, 33-34 and 67, for example. Specifically, Short teaches numerous examples of DNA adducts, for

example, (including those with an "alkaline condition") which block or interrupt the amplification process. See page 8. The specification defines "analog" as "a molecule that may *or may not* structurally resemble a naturally occurring molecule, but functions similarly to the naturally occurring molecule." See page 23, lines 6-8. In the instant case, the DNA adducts, for example, may not structurally resemble a dideoxynucleotide, but functions similarly to the dideoxynucleotide, as it functions to block or interrupt amplification. Furthermore, Short teaches the use of nucleotide analogs (including at least one ribonucleotide, e.g., 5-bromouracil) that can also be used to block or interrupt amplification. See pages 33-34 and 67. Again, even if these analogs are structurally different, they function similarly to dideoxynucleotides. Finally, Short teaches that chain terminators are used to block or interrupt polynucleotide synthesis or amplification. See page 67. Dideoxynucleotides are considered to be "chain terminators." See, for example, Rosenthal et al. (USPN 6,087,095, col. 5, lines 38-54, previously cited), and Monforte et al. (USPN 5,830,655, col. 9, lines 39-40 and col. 35, line 39) who teach that dideoxynucleotides are chain terminators.

It is also noted that Short teaches the removal of DNA adducts for further processing, and that an example of a DNA adduct is a chain terminator. See pages 8 and 68. Furthermore, as stated above, Short clearly teaches using chain terminators (i.e., dideoxynucleotides) for interrupting nucleic acid sequence extension. See pages 67-68, for example. In addition, Short also teaches performing subsequent extension reactions following the interrupting step. See page 7, for example. Accordingly, Short teaches using chain terminators (i.e., dideoxynucleotides) in halting nucleic acid sequence extension (e.g., interruption step), the removal of DNA adduct (e.g., chain terminators), and performing subsequent extension reactions following the

interruption step. Short does not specifically exemplify the removal of dideoxynucleotides or dideoxynucleotide analogs.

However, it would have been obvious to one of skill in the art that by adding a chain terminator to the extension reaction, the chain terminator will be incorporated into the extension product, and chain elongation will terminate. Furthermore, it would have been obvious to one of skill in the art that if subsequent extension reactions were desired to be performed, the chain terminator (e.g., terminal nucleotide) must be removed or modified.

Short '974 teaches that modifying or removing a terminal nucleotide by Exonuclease III ("Exo III") enables subsequent extension reactions. See col. 157-159. Specifically, Short teaches Exo III treatment can be used in conjunction with shuffling, assembling &/or reassembling, recombining and fragmentation methods. See col. 158-159, for example. See also col. 35-40, for example. As stated below, Exo III is an exonuclease well known in the art for removing chain terminators (e.g., dideoxynucleotides). See e.g., teachings of Rosenthal.

Accordingly, in view of the teachings of Short '974, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short '581 so as to have modified or removed the chain terminator (i.e., dideoxynucleotide), in order to have achieved the benefit of providing additional cycles of nucleic acid extension for producing a plurality of polynucleotides that encode a polypeptide of interest.

Short '581 teaches additional series of denaturing, annealing and performing extension. See pages 6-7 and 31, for example. Short '581 also teaches the polynucleotides can be of a different size and sequence. See pages 67, 7-9, 15-18 and 27-35. Short '581 further teaches the

method produces a plurality of extended nucleic acids comprising extension ladders. See pages 6-7, for example.

15. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carr et al. (US 2001/0044111 A1), as applied to claims 1, 4-7, 9, 12-17, 21-22, 29-30, 32, 34-41, 43-44, 47 and 57 above, and further in view of Rosenthal et al. (USPN 6,087,095).

The teachings of Carr are presented above and are incorporated herein. Carr teaches the claimed method comprising adding at least one dideoxynucleotide, and then removing said didexoynucleotide. Carr does not teach using an exonuclease.

However, Rosenthal teaches the removal of chain terminators (e.g., dideoxynucleotides) can be accomplished by using Exo III. See col. 5, lines 49-51 and col. 6, lines 59-64.

Accordingly, in view of the teachings of Rosenthal, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Carr so as to have removed the chain terminators (i.e., dideoxynucleotides) by using Exo III, in order to have achieved the benefit of providing additional cycles of nucleic acid extension.

16. Claims 19, 23-28, 31, 33 and 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carr et al. (US 2001/0044111 A1), as applied to claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-41 43-44, 47 and 57 above, and further in view of Gelfand et al. (USPN 6,346,379).

The teachings of Carr are presented above and are incorporated herein. Carr teaches a number of approaches that can be used to produce "fragmented" nucleic acids. See above. Specifically, Carr teaches these approaches may be accomplished by the incorporation of modified nucleotides (e.g., dideoxynucleotides, ribonucleotides, etc.), enzymatic and chemical

treatments, etc. While Carr teaches the use of various modified nucleotides, Carr does not exemplify the use of α-phosphorothioate nucleotide, a modified nucleotide.

However, Gelfand teaches a α-phosphorothioate nucleotide is a modified or unconventional nucleotide that is the functional equivalent of a terminator, ddNTP, ribonucleotide or other modified or unconventional nucleotide. See col. 6, line 58 to col. 7, line 8, for example.

Accordingly, in view of the teachings of Gelfand, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Carr so as to have used a α-phosphorothioate nucleotide, in order to have achieved the benefit of producing "fragmented" nucleic acids for use in producing a plurality of polynucleotides that encode a polypeptide of interest.

With respect to Claims 19, 23 and 31 (and the dependent claims thereof), it is an inherent property of α-phosphorothioate nucleotides that when incorporated, these modified nucleotides are resistant to cleavage and/or exonuclease degradation. See Nikiforov et al. (USPN 5,518,900) at col. 4, line 56 to col. 5, line 33; col. 12, line 65 to col. 13, line 24; and col. 13, lines 51-64. See also e.g., Rosenthal at col. 6, line 65 to col. 7, line 14, for example.

16. Claims 19, 23-28, 31, 33 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS) in view of Short et al. (USPN 6,361,974), as applied to claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-40, 43-44 and 47 above, and further in view of Gelfand et al. (USPN 6,346,379).

The teachings of Short '581 and Short '974 are presented above and are incorporated

herein. The references teach a number of approaches that can be used to produce "fragmented" nucleic acids. See above. Specifically, the references teach these approaches may be accomplished by the incorporation of modified nucleotides (e.g., dideoxynucleotides, ribonucleotides, etc.), enzymatic and chemical treatments, etc. While the references teach the use of various modified nucleotides (e.g., chain terminators, dideoxynucleotides), the references do not exemplify the use of a α-phosphorothioate nucleotide.

However, Gelfand teaches a α-phosphorothioate nucleotide is a modified or unconventional nucleotide that is the functional equivalent of a terminator, ddNTP, ribonucleotide, or other modified or unconventional nucleotides. See col. 6, line 58 to col. 7, line 8, for example.

Accordingly, in view of the teachings of Gelfand, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short '581 and Short '974 so as to have used a α-phosphorothioate nucleotide, in order to have achieved the benefit of producing "fragmented" nucleic acids for use in producing a plurality of polynucleotides that encode a polypeptide of interest.

With respect to Claims 19, 23 and 31 (and the dependent claims thereof), it is an inherent property of α-phosphorothioate nucleotides that when incorporated, these modified nucleotides are resistant to cleavage and/or exonuclease degradation. See Nikiforov et al. (USPN 5,518,900) at col. 4, line 56 to col. 5, line 33; col. 12, line 65 to col. 13, line 24; and col. 13, lines 51-64. See also e.g., Rosenthal at col. 6, line 65 to col. 7, line 14, for example.

17. Claims 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS) in view of Short et al. (USPN 6,361,974), as applied to claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-40, 43-44 and 47 above, and further in view of Mills (USPN 5,064,754).

The teachings of Short '581 and Short '974 are presented above and are incorporated herein. The references teach treating an extension product in order to modify or remove a ribonucleotide (e.g., by an exonuclease). The references do not teach treating with alkaline phosphatase and an exonuclease or a ribonuclease.

However, modifying or removing a ribonucleotide via treatment with alkaline phosphatase and an exonuclease is well known in the art as taught by Mills. See col. 28. Mills also teaches that ribonuclease can be used. See col. 28.

Accordingly, in view of the teachings of Mills, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have substituted the treatment method of Short '581 and Short '974, for the treatment method of Mills of alkaline phosphatase and an exonuclease, in order to have achieved the benefit of modifying or removing a ribonucleotide for further extension cycles.

18. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carr et al. (US 2001/0044111 A1), as applied to claims 1, 4-7, 9, 12-17, 21-22, 29-30, 32, 34-41, 43-44, 47 and 57 above, and further in view of Mills (USPN 5,064,754).

The teachings of Carr are presented above and are incorporated herein. Carr teaches treating an extension product in order to remove a ribonucleotide (e.g., by uracil N-glycosylase and endonuclease). Carr does not teach treating with alkaline phosphatase and an exonuclease.

However, modifying or removing a ribonucleotide via treatment with alkaline phosphatase and an exonuclease is well known in the art as taught by Mills. See col. 28.

Accordingly, in view of the teachings of Mills, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have substituted the treatment method of Carr, for the treatment method of Mills of alkaline phosphatase and an exonuclease, in order to have achieved the benefit of modifying or removing a ribonucleotide for further extension cycles.

19. Claims 46 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS) in view of Short et al. (USPN 6,361,974), in view of Gelfand et al. (USPN 6,346,379), as applied to claims 19, 23-28, 31, 33 and 45, and in further view of Gish et al. (Nuc. Acid Res. (1987) 18: 253-256, cited in the IDS).

The teachings of Short '581, Short '974 and Gelfand are presented above and are incorporated herein. The references teach using α-phosphorothioate nucleotides for producing "fragmented" nucleic acids. Furthermore, the references teach that in order to perform subsequent rounds of recombination, cleavage of modified nucleotides may occur. The references do not teach cleaving α-phosphorothioate nucleotides by alkylation.

However, Gish teaches that following α-phosphorothioate nucleotide treatment it is advantageous to perform alkylation in order to cleave the α-phosphorothioate nucleotide treated nucleic acid sequence. See page 253, for example.

Accordingly, in view of the teachings of Gish, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short '581, Short '974 and Gelfand so as to have performed alkylation (i.e., cleavage) following α-

phosphorothioate nucleotide treatment, in order to have achieved the benefit of performing subsequent rounds of recombination.

20. Claims 46 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carr et al. (US 2001/0044111 A1), in view of Gelfand et al. (USPN 6,346,379), as applied to claim 45 above, and further in view of Gish et al. (Nuc. Acid Res. (1987) 18: 253-256, cited in the IDS).

The teachings of Carr and Gelfand are presented above and are incorporated herein. The references teach using α-phosphorothioate nucleotides for producing "fragmented" nucleic acids. Furthermore, Carr teaches that in order to perform subsequent rounds of recombination, cleavage of modified nucleotides may occur. The references do not teach cleaving α-phosphorothioate nucleotides by alkylation.

However, Gish teaches that following α-phosphorothioate nucleotide treatment it is advantageous to perform alkylation in order to cleave the α-phosphorothioate nucleotide treated nucleic acid sequence. See page 253, for example.

Accordingly, in view of the teachings of Gish, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Carr and Gelfand so as to have performed alkylation (i.e., cleavage) following α-phosphorothioate nucleotide treatment, in order to have achieved the benefit of performing subsequent rounds of recombination.

21. Claims 48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS) in view of Short et al. (USPN 6,361,974), as applied to claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-40, 43-44 and 47 above, and further in view of Wong et al. (USPN 5,935,793) or Nikiforov et al. (USPN 5,518,900).

The teachings of Short '581 and Short '974 are presented above and are incorporated herein. The references teach a number of approaches that can be used to produce "fragmented" nucleic acids. See above. Specifically, the references teaches these approaches may be accomplished by the incorporation of modified nucleotides (e.g., dideoxynucleotides, ribonucleotides, etc.), chain termination methods, enzymatic and chemical treatments, etc. While the references teach the use of various modified nucleotides (e.g., dideoxynucleotides), the references do not exemplify the use of the Maxam Gilbert treatment.

However, Wong (and Nikiforov) teach the Maxam and Gilbert treatment is a functional equivalent of using a length-altering agent, such as a dideoxynucleotide. See Wong at col. 17, lines 3-9, and Nikiforov at col. 5-6. Specifically, the uses of dideoxynucleotides (e.g., in a Sanger method) and the Maxam and Gilbert treatment have been well known in the art as equivalents for performing extension reactions and terminating said reactions to produce nucleic acid sequence fragments. See Wong and Nikiforov.

Accordingly, in view of the teachings of Wong (or Nikiforov), it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short '581 and Short '974 so as to have used a Maxam and Gilbert, in order to have achieved the benefit of producing "fragmented" nucleic acids for use in producing a plurality of polynucleotides that encode a polypeptide of interest.

22. Claims 48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carr et al. (US 2001/0044111 A1), as applied to claims 1, 4-7, 9, 12-19, 21-41 43-44, 47 and 57 above, and further in view of Wong et al. (USPN 5,935,793) or Nikiforov et al. (USPN 5,518,900).

The teachings of Carr are presented above and are incorporated herein. Carr teaches

a number of approaches that can be used to produce "fragmented" nucleic acids. See above. Specifically, Carr teaches these approaches may be accomplished by the incorporation of modified nucleotides (e.g., dideoxynucleotides, ribonucleotides, etc.), chain termination methods, enzymatic and chemical treatments, etc. While Carr teaches the use of various modified nucleotides (e.g., dideoxynucleotides), Carr does not exemplify the use of the Maxam Gilbert treatment.

However, Wong (and Nikiforov) teach the Maxam and Gilbert treatment is a functional equivalent of using a length-altering agent, such as a dideoxynucleotide. See Wong at col. 17, lines 3-9, and Nikiforov at col. 5-6. Specifically, the uses of dideoxynucleotides (e.g., in a Sanger method) and the Maxam and Gilbert treatment have been well known in the art as equivalents for performing extension reactions and terminating said reactions to produce nucleic acid sequence fragments. See Wong and Nikiforov.

Accordingly, in view of the teachings of Wong (or Nikiforov), it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Carr so as to have used a Maxam and Gilbert, in order to have achieved the benefit of producing "fragmented" nucleic acids for use in producing a plurality of polynucleotides that encode a polypeptide of interest.

Conclusion

23. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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October 29, 2004

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